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Abstract

B-Chlorodiisopinocampheylborane (DIP-Chloride) introduced by us several years ago is an excellent reagent for the asymmetric reduction of aralkyl and α-hindered ketones. We have now shown that this reagent is extremely efficient for the reduction of aryl and alkyl perfluoroalkyl ketones, including α'-perfluoroalkyl α-acetylenic ketones, generally providing ≥90% ee for the product alcohols. A systematic study of the electronic and steric influence in the reduction of fluoroalkyl ketones with DIP-Chloride and *B*-isopiocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane), and a comparison of the reduction of fluoroalkyl ketones with that of the corresponding chloroalkyl ketones have been made. The compatibility of DIP-Chloride with different functional groups substituted in the phenyl ring of acetophenone has been studied. The results show that most groups are compatible with the reagent. However, *ortho*-hydroxyl and carboxyl substitutions result in the opposite configuration for the product alcohol, probably due to a chelation followed by intramolecular reduction. DIP-Chloride reacts with *o*,*o*-disubstituted acetophenones with reduced rate and decreased ee for the product alcohols. The utility of DIP-Chloride in the syntheses of optically pure pharmaceuticals, such as an analog of BMS-181100 and eprozinol has been demonstrated. Studies to prepare new and improved asymmetric reducing reagents led to diiso-2-β-chloroethylapopinocampheylborane ($Cleap_2BCl$). This reagent reduces representative ketones of 8 of the 10 classes to the corresponding *sec*-alcohols in excellent ee.

SUPER HYDRIDES

FINAL REPORT

Herbert C. Brown

Principal Investigator

July 15, 1991 - July 31, 1994

U. S. Army Research Office

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I. List of Participating Persons.

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A. V. Teodorovic'	7/15/91 - 9/30/93
B. G. Gong	1/01/93 - 7/31/94
G. M. Chen	9/14/93 - 7/31/94
G. Li	4/01/94 - 7/31/94

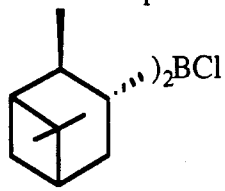
II. Significant Results.

During this project period, we concentrated our efforts in three directions in the area of asymmetric reduction: (1) exploration of the merits and limits of DIP-Chloride, (2) application of DIP-Chloride to the synthesis of optically pure pharmaceuticals, and (3) development of new chiral reducing agents. The results achieved during this period were presented in six symposia/workshop and 14 publications. They are summarized below.

1. Explorations of the Merits and Limits of DIP-Chloride.

(a) Asymmetric reduction of alkyl (aryl) perfluoroalkyl ketones.

B-Chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™, **1**) is an excellent reagent for the chiral reduction of aralkyl and α-hindered ketones.[1] Due to the importance of fluoroalkyl compounds in agricultural, materials, medicinal, and organic chemistry, we concentrated our attention on the asymmetric reduction of perfluoroalkyl ketones with **1** and the study of the effect of mono- and difluoromethyl groups on asymmetric reduction as compared to the perfluoroalkyl group. We found



(–)-DIP-Chloride™, **1**

that the reduction of all of the perfluoroalkyl ketones always provide the corresponding optically active alchols in very high ee (Table 1).[2]

For example, 2,2,2-trifluoroacetophenone, trifluoroacetyl-1-naphthalene, and trifluoroacetyl-2-naphthalene are all reduced with **1** within 1-3 d at rt in 90% ee, 78% ee and 91% ee, respectively. The optical purity of 1-phenyl-2,2,2-trifluoroethanol is upgraded to ≥99% ee by crystallizing the initially formed product from pentane. 1,1,2,2,2-Pentafluoropropiophenone and 1,1,2,2,3,3,3-heptafluorobutyrophenone are reduced in 3 d with **1** to the corresponding alcohols in 92% ee and 87% ee, respectively. The reagent reduces alkyl trifluoromethyl ketones at a rate faster than that of the aryl derivatives, while still providing the product alcohols in very high ee. Thus, 1,1,1-trifluoroacetone, 1,1,1-trifluorononan-2-one, and 1,1,1-trifluorodecan-2-one are all reduced within 4-8 h in 89% ee, 92% ee, and 91% ee, respectively. Even α-*sec*-alkyl trifluoromethyl ketones are

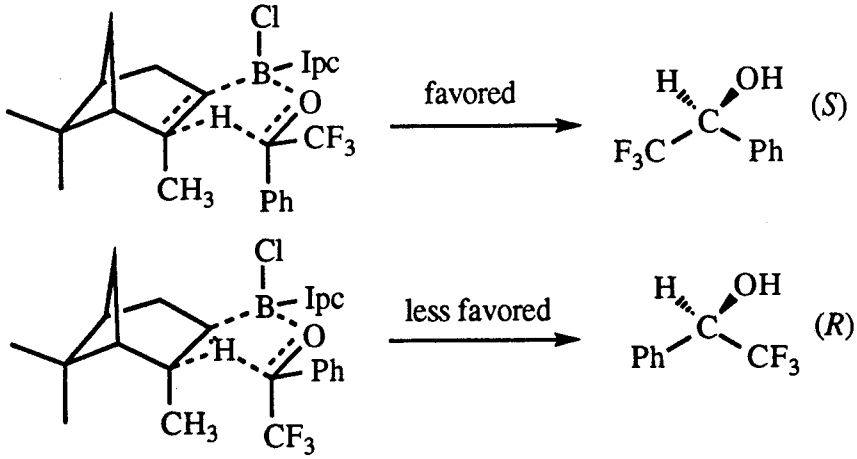
handled by **1** very efficiently. Thus cyclohexyl trifluoromethyl ketone is reduced by **1** at rt in 12 h to the product alcohol in 87% ee. The results are summarized in Table 1.

Table 1. Asymmetric reduction of aryl or alkyl perfluoroalkyl ketones with (–)-DIP-Chloride at 25 °C

ketone	R-CO-R_F R	R_F	react time, h	yield, isol.	$[\alpha]_D$	% ee[a]	isomer
1	Ph	CF_3	24	90	+37.64° (neat)[b]	90	*S*
2	1-Naphth	CF_3	72	93	+20.35° (*c* 5.17, EtOH)	78	*S*
3	2-Naphth	CF_3	72	92	+35.1° (*c* 4.14, EtOH)	91	*S*
4	9-anthryl	CF_3	30 d[c]	48	+24.61° (*c* 6.1, $CHCl_3$)	82	*S*
5	Ph	C_2F_5	72	82	+28.95° (*c* 2.69, EtOH)	92	*S*
6	Ph	C_3F_7	72	81	+23.02° (*c* 2.32, EtOH)	87	*S*
7	CH_3	CF_3	3	70	– 5.60° (neat)	89	*S*
7	CH_3	CF_3	96	72	– 6.24° (neat)	96[d]	*S*
8	*n*-C_7H_{15}	CF_3	8	80	–23.35 (*c* 2.6, $CHCl_3$)	92	*S*
9	*n*-C_8H_{17}	CF_3	8	87	–20.44° (*c* 3.84, MeOH)	91	*S*
10	Chx	CF_3	12	75	–17.82° (*c* 7.5, $CHCl_3$)	87	*S*
11	*t*-Bu	CF_3	very slow reaction				

[a] ee determined as their MTPA or MCF derivative on a capillary GC. [b] α_D^{25}. On crystallization from pentane at 0 °C. α_D^{22} improved to +42.18° which corresponds to ≥99% ee. [c] 60% reaction was complete in 30 d. [d] For a reaction at –25 °C.

In all of these cases the trifluoromethyl group acts as the enantiocontrolling larger group as compared to the aryl or alkyl group. This produces alcohol products with stereochemistry opposite to those obtained for the corresponding hydrogen analogs (Scheme 1).



Scheme 1. Tentative mechanism of reduction of perfluoroalkyl ketones with DIP-Chloride

(b) Systematic study of the asymmetric reduction of fluoroalkyl ketones

The above study revealed that DIP-Chloride is an excellent reagent for the reduction of perfluoroalkyl ketones. At present, this is the only reagent that can reduce this class of ketone with this consistency in such high ee. However, the corresponding trialkylborane reagent, (–)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane®, **2**) fails to reduce this class of ketone in high ee. A systematic study of the asymmetric reduction of aryl and alkyl α-fluoroalkyl ketones with (–)-DIP-Chloride and *R*-Alpine-Borane was made. In the case of reagent **1**, the direction of asymmetric induction in the chiral reduction of aryl trifluoromethyl ketones differs from that of the corresponding mono- and difluoromethyl ketones. For example, while 2-fluoro, and 2,2-difluoroacetophenones are reduced with **1** to the *R*-alcohols in 95% and 85% ee, respectively, 2,2,2-trifluoroacetophenone is reduced, under neat conditions at room temperature, to the *S*-alcohol in 90% ee. Though DIP-Chloride reduces unhindered prochiral dialkyl ketones in poor ee, alkyl α-fluoroalkyl ketones are reduced in improved ee depending on the number of α-fluorine atoms present in the ketone. While monofluoromethyl ketones provide moderate ee in the *R*-isomer, the di- and trifluoromethyl ketones are reduced in moderate to excellent ee in the opposite isomer. For example, 1-fluoro-2-octanone is reduced in 40% ee (*R*), whereas 1,1-difluoro- and 1,1,1-trifluoro-2-octanone are reduced in 32% (*S*), and 91% ee (*S*), respectively. In the case of the asymmetric reduction of the above series of ketones with **2**, the results are different. There is no change in the direction of chiral induction in the reduction of α-fluoroacetophenones with **2**. 2-Fluoroacetophenone and 2,2-difluoroacetophenone are reduced with **2** to the *R*-alcohol in 89% and 97% ee, respectively. The reaction of 2,2,2-trifluoroacetophenone is very slow, only 90% complete in 45 d, and provides the *R*-alcohol in 32% ee. In contrast, while 1-fluoro- and 1,1-difluoro-2-octanone are reduced by **2** in 65% (*R*) and 50% ee (*R*), respectively, 1,1,1-trifluoro-2-octanone is reduced in 60% ee (*S*), raising the question of which factors other than the steric size of the trifluoromethyl group, control the enantioselectivity of these reductions. The results are summarized in Tables 2 and 3.[3]

Table 2. Asymmetric reduction of fluoroalkyl ketones with (–)-DIP-Chloride at –25 °C

ketone	R-CO-R_F R	R_F	react time, h	yield, isol.	%ee[a]	isomer	enantiocontrolling group preference[b]
1	Ph	CH_3	5	72	98	*S*	Ph > CH_3
2	Ph	CH_2F	1	80	95	*R*[c]	Ph > CH_2F
3	Ph	CHF_2	0.5	60	85	*R*[c]	Ph > CHF_2
4	Ph	CF_3	24[d]	90	90	*S*[e]	CF_3 > Ph
5	*n*-C_6H_{13}	CH_3	5	72	7	*R*	CH_3 > *n*-Hex
6	*n*-C_6H_{13}	CH_2F	6	72	40	*R*	*n*-Hex > CH_2F
7	*n*-C_6H_{13}	CHF_2	6	72	32	*S*	CHF_2 > *n*-Hex
8	*n*-C_6H_{13}	CF_3	8[d]	74	91	*S*	CF_3 > *n*-Hex

[a] ee determined as their MTPA derivative on a capillary GC. [b] Based on the proposed mechanism of the reduction (ref. 1). [c] The *R*-configuration is a consequence of the Cahn-Ingold-Prelog rules. [d] For a reaction at rt. [e] The *S*-configuration is a consequence of the Cahn-Ingold-Prelog rules.

Table 3. Asymmetric reduction of fluoroalkyl ketones with *R*-Alpine-Borane at 25 °C

ketone	R-CO-R_F R	R_F	react time, d	yield, isol.	%ee[a]	isomer	enantiocontrolling group preference[b]
1	Ph	CH_3	14	80	87	*S*	Ph > CH_3
2	Ph	CH_2F	4	71	89	*R*[c]	Ph > CH_2F
3	Ph	CHF_2	4	69	97	*R*[c]	Ph > CHF_2
4	Ph	CF_3	45	57	32	*R*[c]	Ph > CF_3
5	*n*-C_6H_{13}	CH_3	7	70	48	*S*	*n*-Hex > CH_3
6	*n*-C_6H_{13}	CH_2F	9	82	65	*R*	*n*-Hex > CH_2F
7	*n*-C_6H_{13}	CHF_2	10	78	50	*R*	*n*-Hex > CHF_2
8	*n*-C_6H_{13}	CF_3	14	72	60	*S*	CF_3 > *n*-Hex

[a] ee determined as their MTPA derivative on a capillary GC. [b] Based on the tentative mechanism of the reduction. [c] The *R*-configuration is a consequence of the Cahn-Ingold-Prelog rules.

(c) Asymmetric reduction of acetylenic fluoroalkyl ketones

Unlike Alpine-Borane, DIP-Chloride is a poor reagent for the chiral reduction of α-acetylenic ketones. However, a systematic study of the asymmetric reduction of prochiral α-acetylenic α'-fluoroalkyl ketones with (–)-*B*-chlorodiisopinocampheylborane [(–)-DIP-Chloride, **1**] and (–)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane, **2**) reveals that perfluoroalkyl

acetylenic ketones can be reduced in very high ee (92-≥99%) with both of these reagents. For example, 1,1,1-trifluoro-4-phenyl-3-butyn-2-one, 1,1,1,2,2-pentafluoro-5-phenyl-4-pentyn-3-one, and 4,4,5,5,6,6,6-heptafluoro-1-phenyl-1-hexyn-3-one are all reduced with **1** in EE at –25 °C within 0.25-2 h in 98%, 96%, and 94% ee, respectively. The same ketones are reduced with **2** under neat condition, within 1-4 h at rt in 98%, 97%, and 96% ee, respectively. Similarly, 1,1,1-trifluoro-3-octyn-2-one, 1,1,1,2,2-pentafluoro-4-nonyn-3-one, and 1,1,1,2,2,3,3-heptafluoro-5-decyn-4-one are reduced with both **1** and **2** in ≥97% ee. Difluoromethyl and monofluoromethyl acetylenic ketones are reduced with **2** in relatively high ee (78-88% ee) whereas **1** is ineffective for these types of ketones. In all of the above reductions, the fluoroalkyl group acts as the enantiocontrolling group with one exception. A remarkable inversion in selectivity in the reduction of monofluoromethyl acetylenic ketones with **1** is observed as compared to the reduction with **2**, indicating that in the transition state the acetylenic moiety acts as the enantiocontrolling group instead of the anticipated monofluoromethyl group. These results highlight the combined effects of both the electronic and steric influences of the fluorine in controlling both the rate and the enantioselectivity in the asymmetric reduction of prochiral fluorinated acetylenic ketones. The results are summarized in Table 4.[4]

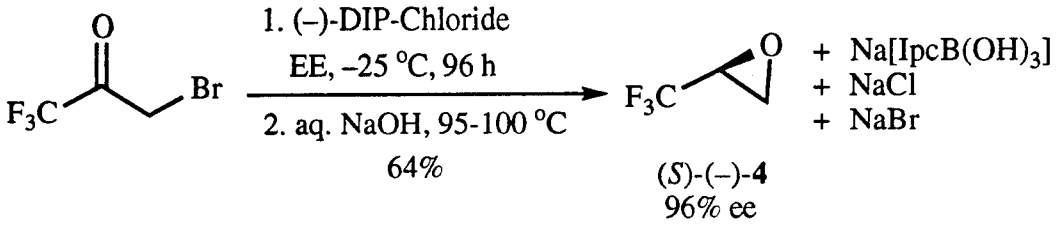
Table.4 Asymmetric reduction of fluoroalkyl alkynyl ketones with (–)-DIP-Chloride and (*R*)-Alpine-Borane

ketone reduced	R-C≡C-CO-R_F R	R_F	DIP-Chloride Rn time, h	%Yield	% ee[a]	Alpine-Borane Rn time, h	%Yield	% ee[a]
1	Ph	CF_3	0.25	81	98	1	89	98
2	Ph	C_2F_5	2	77	96	4	90	97
3	Ph	C_3F_7	2	78	94	4	88	96
4	Ph	CHF_2	2	84	38	4	87	82
5	Ph	CH_2F	2	88	28	4	91	78
6	*n*-Bu	CF_3	1	76	≥99	2	78	98
7	*n*-Bu	C_2F_5	2	72	96	4	80	98
8	*n*-Bu	C_3F_7	2	72	92	4	82	98
9	*n*-Bu	CHF_2	2	74	15	4	80	88
10	*n*-Bu	CH_2F	2	79	46	4	89	78

[a]Analyzed as the MTPA ester on a capillary GC.

(d) A One-pot synthesis and ring-cleavage reactions of the enantiomers of trifluoromethyloxirane.

We took advantage of the capability of DIP-Chloride to reduce perfluoroalkyl ketones in high ee by designing an extremely efficient one-pot asymmetric synthesis of either enantiomer of trifluoromethyloxirane (3,3,3-trifluoro-1,2-epoxypropane, **4**) in 64% yield and 96% ee *via* the asymmetric reduction of the commercially available 1-bromo-3,3,3-trifluoro-2-propanone with either (+)- or (–)-DIP-Chloride, followed by ring closure of the intermediate chloroborinate, IpcBCl[OCH(CH_2Br)CF_3].



The ring cleavage reactions of **4** provide a general synthesis of chiral trifluoromethyl carbinols without loss of optical activity. Thus we have synthesized 1-amino-3,3,3-trifluoro-2-propanol, 1-azido-3,3,3-trifluoro-2-propanol, 1-diethylamino-3,3,3-trifluoro-2-propanol, 1-cyano-3,3,3-trifluoro-2-propanol, 1,1,1-trifluoro-2-propanol, 1,1,1-trifluoro-2-octanol, 1-phenyl-3,3,3-trifluoro-2-propanol, 1-ethoxy-3,3,3-trifluoro-2-propanol, and 1,2-dihydroxy-3,3,3-trifluoropropane, in 61-88% yields and in 96% ee by the cleavage of **4** with the appropriate nucleophile. The results are summarized in Table 5.[5]

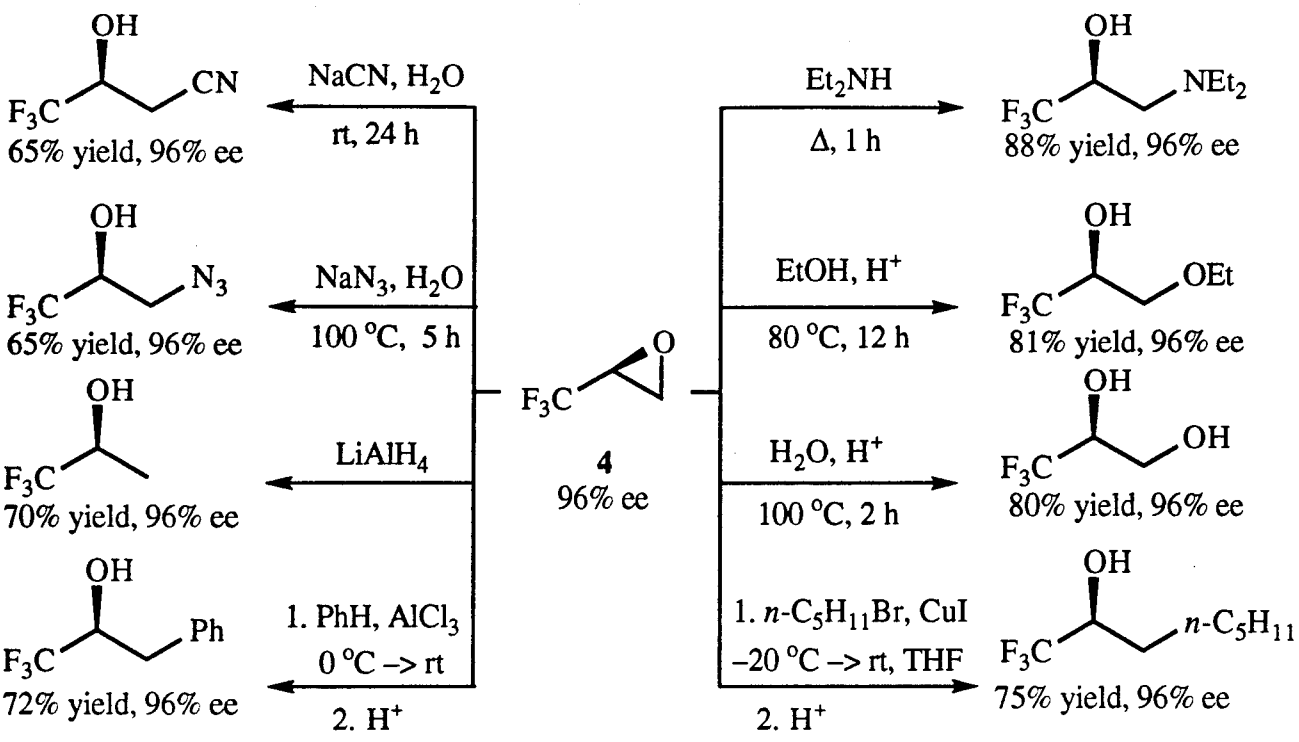


Table 5. Ring-cleavage reactions of (*S*)-trifluoromethyloxirane

reagent	product	react. temp. °C	react. time, h	yield %	$[\alpha]_D$	ee %	config.[a]
$KN(SiMe_3)_2$	$CF_3CH(OH)CH_2NH_2$	25	12	61	–19.54 (*c* 1.3, MeOH)	≥99[b,c]	*S*
NaN_3	$CF_3CH(OH)CH_2N_3$	25	5	65	+12.87 (*c* 1.9, MeOH)	96[d]	*S*
Et_2NH	$CF_3CH(OH)CH_2NEt_2$	55	1	88	–29.79 (*c* 1.4, MeOH)	96[e]	*S*
NaCN	$CF_3CH(OH)CH_2CN$	25	12	65	–16.78 (*c* 1.5, MeOH)	96[f]	*S*
$LiAlH_4$	$CF_3CH(OH)CH_3$	25	1.5	70	–6.24 (neat)	96[e]	*S*
n-$C_5H_{11}MgBr$	$CF_3CH(OH)C_6H_{13}$	–20-25	3	75	–25.52 (*c* 1.5, $CHCl_3$)	96[b]	*S*
PhH, $AlCl_3$	$CF_3CH(OH)CH_2Ph$	0-25	3	72	–50.24 (*c* 1.8, MeOH)	96[f]	*S*
$EtOH/H^+$	$CF_3CH(OH)CH_2OEt$	80	12	81	–11.20 (*c* 1.4, MeOH)	96[f]	*S*
H_2O/H^+	$CF_3CH(OH)CH_2OH$	100	2	80	–10.95 (*c* 1.4, MeOH)	96[f]	*S*

[a] Based on the reaction mechanism. [b] Determined as the MTPA ester on a SPB-5 capillary column. [c] The initial product was crystallized in EE. [d] Determined by converting the azide to the amine. [e] Determined as the MCF derivative on a SPB-5 capillary column. [f] Determined as the TFA derivative on a Chiraldex-GTA column.

(e) Asymmetric reduction of alkyl (aryl) haloalkyl ketones.

It was desirable to have a comparison of the reduction of aryl and alkyl chloroalkyl ketones and the corresponding fluoroalkyl ketones to determine whether perchloroalkyl ketones can be also reduced to the product alcohols with equally high asymmetric induction and opposite configuration. Moreover, trichloromethyl alcohols can be utilized in the synthesis of α-amino acids. Accordingly, we continued our explorations on the asymmetric reduction of haloketones with DIP-Chloride and Alpine-Borane. We reduced alkyl and aryl chloroalkyl ketones with **1** and **2** and compared the results with the reduction of the corresponding fluoroketones (Table 6). The results show the influence of electronic and steric factors in asymmetric reduction with DIP-Chloride.

Table 6. Asymmetric reduction of halo-ketones with Alpine-Borane and (–)-DIP-Chloride

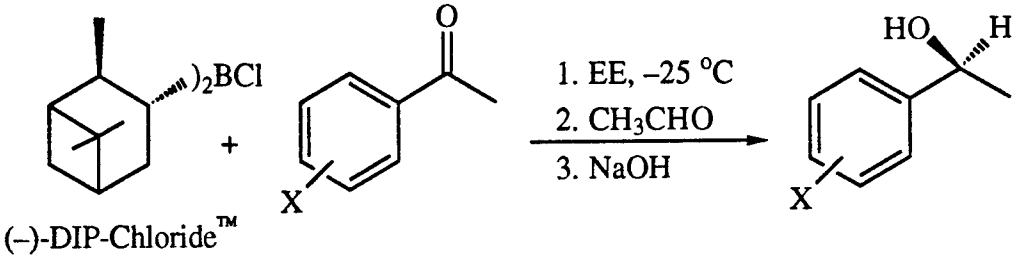
ketone	R-CO-R'		% ee[a]	
	R	R'	Alpine-Borane	DIP-Chloride
1	CH_3	CCl_3	7	97
2	CH_3	CF_3	81	96
3	CH_3	$CHCl_2$	58	13
4	CH_3	CHF_2	16	5
5	CH_3	CH_2Cl	19	15
6	CH_3	CH_2F	13	63
7	Ph	CCl_3	48	71
8	Ph	CF_3	35	90
9	Ph	$CHCl_2$	76	80
10	Ph	CHF_2	97	72
11	Ph	CH_2Cl	96	95
12	Ph	CH_2F	88	95

[a] ee determined as their MTPA or MCF derivative on a capillary GC.

(f) Asymmetric reduction of ring-substituted acetophenones.

DIP-Chloride is an excellent chiral reducing agent for aralkyl, α-hindered and α-trifluoromethyl ketones. This reagent has found wide applications in the pharmaceutical industry. However, a systematic study to ascertain the compatibility of the reagent with various substituents in the phenyl ring had not been done. We made such a study by carrying out the asymmetric reduction

of acetophenones with typical substituents, such as, –OMe, –OH, –Me, –F, –Cl, –Br, –I, –COOR, –CN, $–NO_2$, $–CF_3$, etc., in the *ortho*, *meta*, and *para* positions, by DIP-Chloride. The results are presented in Table 7.



(–)-DIP-Chloride™

Table 7. Asymmetric reduction of ring-substituted acetophenones with (–)-DIP-Chloride

ketone	X-Ph-$COCH_3$ X	react temp	react time, h	yield, isol.	% ee[a]	isomer[b]
1	2-Fluoro	–25 °C	5	75	95	*S*
2	3-Fluoro	–25 °C	6	78	96	*S*
3	4-Fluoro	–25 °C	6	74	96	*S*
4	2-Chloro	–25 °C	5	70	96	*S*
5	3-Chloro	–25 °C	6	75	97	*S*
6	4-Chloro	–25 °C	6	72	98	*S*
7	4-Bromo	–25 °C	5	80	96	*S*
8	4-Iodo	–25 °C	17	60	97	*S*
9	2-Nitro	–25 °C	8	66	96	*S*
10	3-Nitro	–25 °C	8	70	96	*S*
11	4-Nitro	–25 °C	5	75	94	*S*
12	3-Cyano	–25 °C	16	70	96	*S*
13	4-Cyano	–25 °C	16	71	97	*S*
14	2-COOH[c]	25 °C	60	65	25	*R*
15	4-COOH	–25 °C	12	80	97	*S*
16	2-COOMe	–25 °C	8	75	94	*S*
17	4-COOEt	–25 °C	8	65	97	*S*
18	4-$CONH_2$	–25 °C	18	52	95	*S*
19	4-$CONEt_2$	–25 °C	12	50	95	*S*
20	2-Me	–25 °C	7	71	96	*S*
21	3-Me	–25 °C	6	70	96	*S*
22	4-Me	–25 °C	6	80	94	*S*
23	4-*t*-Bu	–25 °C	8	80	96	*S*
24	2-OH[d]	25 °C	36	68	81	*S*
25	3-OH	–25 °C	8	82	97	*S*
26	4-OH	–25 °C	12	50	10	*S*
27	2-OLi[d]	25 °C	36	70	90	*S*
28	4-OLi	–25 °C	12	60	90	*S*
29	2-OMe	–25 °C	8	70	92	*S*
30	3-OMe	–25 °C	8	75	96	*S*

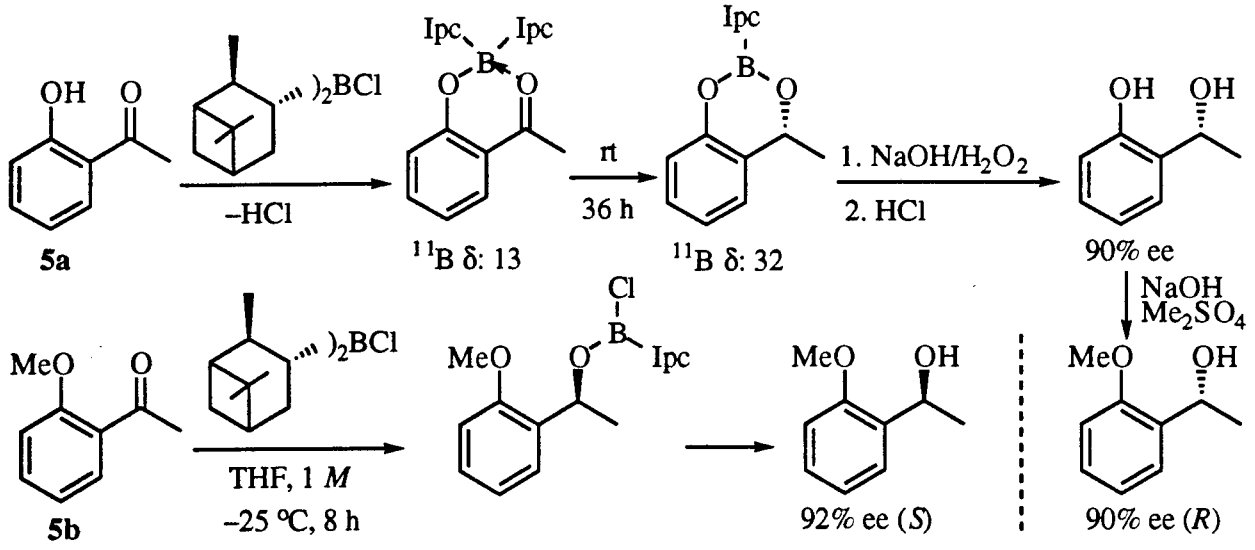
31	4-OMe	–25 °C	14	66	77	*S*
ketone	X-Ph-$COCH_3$ X	react temp	react time, h	yield, isol.	% ee[a]	isomer[b]
32	2-CF_3	–25 °C	7	85	94	*S*
33	3-CF_3	–25 °C	7	82	95	*S*
34	4-CF_3	–25 °C	7	78	96	*S*
35	4-NH_2[c]	–25 °C	24	50	89	*S*
36	4-$NHCOCF_3$	–25 °C	24	80	85	*S*

[a] ee determined as their MTPA or MCF derivative on a capillary GC. [b] determined by comparison of authentic sample or by analogy of earlier results. [c]ketone:reagent ::1:2. [d]reaction proceeds by an initial chelate formation.

(g) Asymmetric reduction of *ortho*-hydroxyacetophenones.

In the above study, we observed that *o*-hydroxyacetophenone undergoes reduction with a different pathway as depicted in the following scheme leading to the product alcohol of opposite configuration as compared to the corresponding *o*-methoxyacetophenone. The reaction is slow at –25 °C due to the chelation and proceeds to completion within 36 h at room temperature.

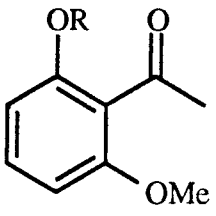
However, Danishefsky had reported in the recent literature[6] a reduction of the ketone shown below, an *o*-hydroxy *o*-carbomethoxyacetophenone, to the product of the expected (*S*)-configuration. To understand this anomaly, we reduced a series of 2'-hydroxyacetophenones. The reduction took place in a different pathway as shown in Scheme 2 and we obtained the product alcohol of opposite configuration in very high ee.[7]



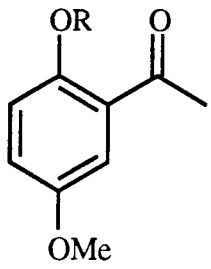
Scheme 2. Asymmetric reduction of 2'-hydroxyacetophenone

To avoid any possible uncertainities in the chiral outcome arising from the HCl liberated during the initial chelation, the lithio salt of the phenolic acetophenone **5a** was treated with DIP-Chloride to achieve the same result without the liberation of HCl. Moreover, the scheme suggests that diisopinocampheylborane, Ipc_2BH,[8] should be as effective as DIP-Chloride in reducing **5a**. Indeed, this is observed experimentally providing product with the same configuration and % ee as that obtained with the corresponding DIP-Chloride.

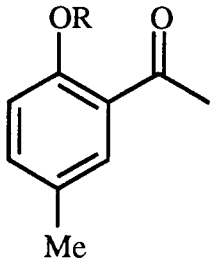
The generality of this opposite stereochemistry from an intramolecular reduction was examined for a series of *o*-hydroxyacetophenones (**6a-11a**) and, following methylation of the *o*-hydroxy group, compared with the product alcohols obtained from the intermolecular reduction of the corresponding *o*-methoxyacetophenones (**6b-11b**). In all cases, the configuration realized was opposite. The results are presented in Table 8.



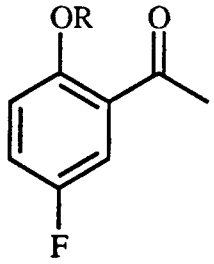
6a, R = H
6b, R = Me



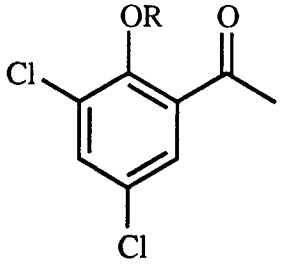
7a, R = H
7b, R = Me



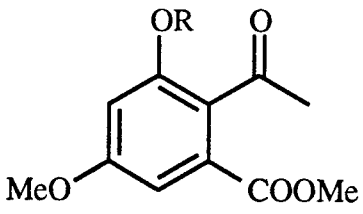
8a, R = H
8b, R = Me



9a, R = H
9b, R = Me



10a, R = H
10b, R = Me



11a, R = H
11b, R = Me

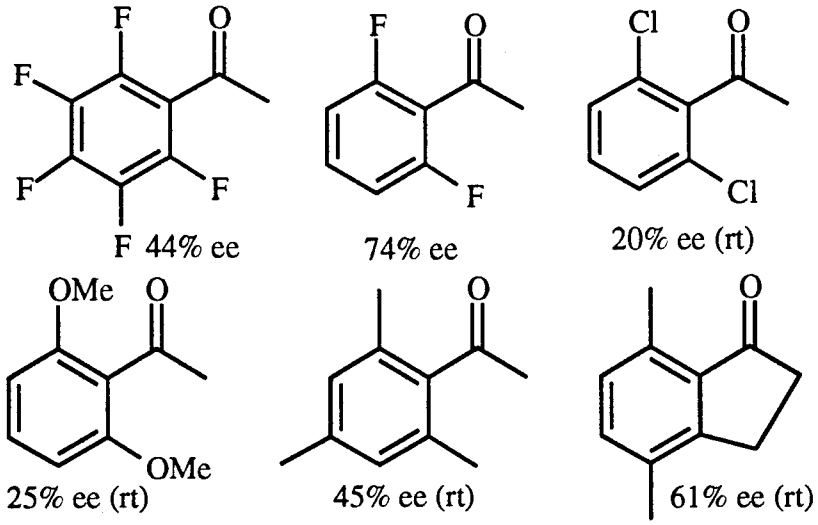
Table 8. Asymmetric reduction of *o*-hydroxy- and *o*-methoxyacetophenones with (–)-DIP-Chloride

ketone	reactn condn	% ee[a]	config	ketone	reactn condn	% ee[a]	config
5a	THF, rt, 36 h	90	*R*	**5b**	THF, –25 °C, 8 h	92	*S*
6a	THF, rt, 48 h	96	*R*[b]	**6b**	THF, 0 °C, 24 h	20	*R*
7a	THF, rt, 48 h	82	*R*[b]	**7b**	THF, –25 °C, 8 h	93	*S*[c]
8a	THF, rt, 48 h	82	*R*[b]	**8b**	THF, –25 °C, 8 h	95	*S*[c]
9a	THF, rt, 12 h	79	*R*[b]	**9b**	THF, –25 °C, 6 h	94	*S*[c]
10a	THF, 0 °C, 6 h	78	*R*[b]	**10b**	THF, –25 °C, 6h	94	*S*[c]
11a	THF, rt, 16 h	90[d]	*R*[b]	**11b**	THF, 0-25 °C, 16 h	20[e]	*S*[c]

[a]Determined by GC analysis as the MTPA ester on a capillary GC. [b] By analogy with the product from **5a**. [c]By analogy with the product from **5b**. [d]The % ee determined by ^{1}H and ^{19}F NMR of the MTPA ester of the *o*-hydroxylactone. The ee was improved to 98% by crystallizing from acetone. [e]By comparison of the rotation with the product derived from **11a**.

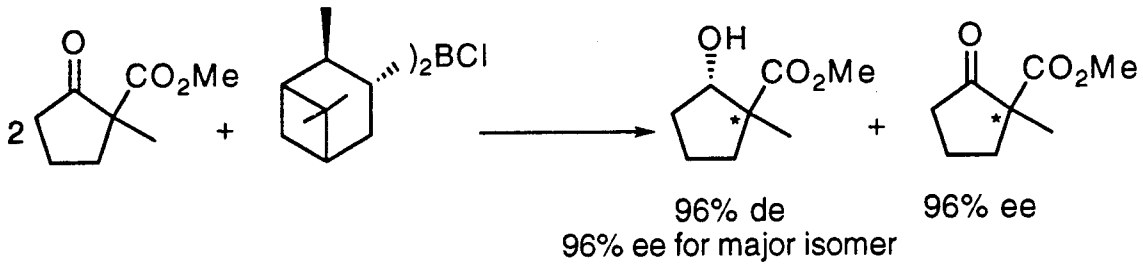
(h) Reduction of *o,o*-disubstituted acetophenones

As part of our study of the applications of DIP-Chloride, we reduced 2',3',4',5',6'-pentafluoroacetophenone and were surprised that we obtained the product in only 44% ee. To understand this anomaly, we reduced a series of mono-, di- and trifluoro-substituted acetophenones and found that *o,o*-disubstitution in acetophenone leads to a decrease in the rate of reduction and the ee of the product alcohols. For example, *o,o*-difluoroacetophenone is reduced under our standard conditions, (–25 °C, EE, 1*M*), in 74% ee. However, the reduction of the corresponding *o,o*-dichloro-, *o,o*-dimethoxy- derivatives were extremely slow at –25 °C and were carried out at rt. Consequently, we studied a series of *o,o*-disubstituted acetophenones all of which gave the product alcohol in poor ee. We are studying this phenomenon using with the aid of molecular mechanics.



(i) Kinetic resolution of racemic α-substituted ketones.

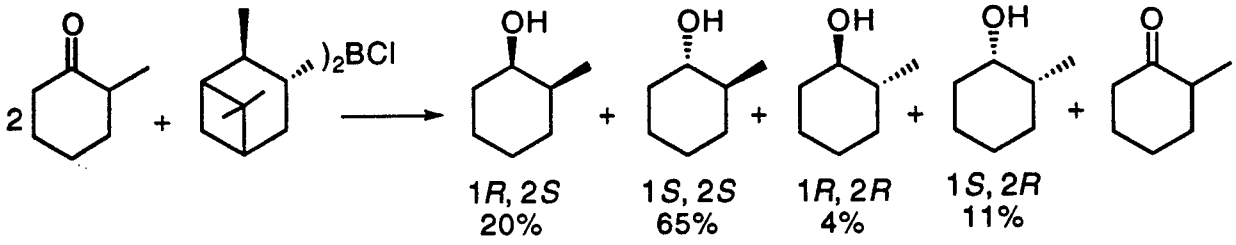
DIP-Chloride is an excellent chiral reducing agent for the reduction of α-tertiary alkyl ketones. We exploited this observation to kinetically resolve α-chiral ketones.



The configrations of the alcohol and the recovered ketone are being determined.

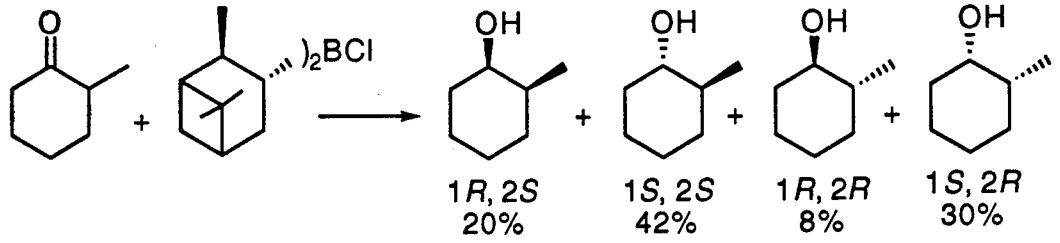
When we applied this reaction to the reduction of 2-methylcyclohexanone, we observed the following interesting features.

1. We obtain the *trans*-alcohol product in excess though the reduction of 2-methylcyclopentanone gave the *cis*-product exclusively.



However, the recovered ketone showed no optical activity.

2. When a 1:1 reaction of 2-methylcyclohexanone with (–)-DIP-Chloride was carried out, we obtained a 1:1 ratio of the *cis* and *trans* products, with the *cis* product showing 22% ee and the *trans* product revealing 70% ee.



The above observations suggest that the ketone undergoes epimerization during the reduction with DIP-Chloride. The results from the 1:1 reduction cannot be accounted for unless 12% of the (*R*)-ketone is epimerized to the (*S*)-ketone.

This observation is being studied very carefully. The results of our study are presented in Tables 9 and 10.

Table 9. Asymmetric reduction of 2-methylcyclohexanone with (–)-DIP-Chloride

DIP-Chloride/ ketone	Product Alcohol, % 1*R*, 2*S*	1*S*, 2*S*	1*R*, 2*R*	1*S*, 2*R*	*cis*/ *trans*	% ee *cis*	*trans*
1:1	20	42	8	30	50/50	22	70
1.2:1	19	37	8	36	55/45	33	66
1:2[a]	29	52	3	16	45/55	31	92
1:2[b]	20	65	4	11	31/69	31	92

[a]Worked up after collecting the α-pinene liberated during the reaction and the excess ketone using vacuum pump.
[b]Worked up immediately after reaction with diethanolamine.

Table 10. Asymmetric reduction of 2-methylcyclohexanone with (+)-DIP-Chloride

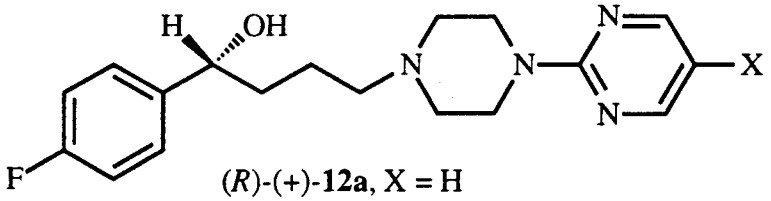
DIP-Chloride/ ketone	Product Alcohol, % 1*R*, 2*S*	1*S*, 2*S*	1*R*, 2*R*	1*S*, 2*R*	*cis*/ *trans*	% ee *cis*	*trans*
1.2:1	35	7	37	21	56/44	24	69
1:2	14	3	55	28	42/58	34	93

2. Applications of DIP-Chloride for the synthesis of optically pure pharmaceuticals.

Synthesis of optically pure products as candidates for drug development is becoming a norm unless justifications are made based on differential activity, disposition and therapeutic need.[9] Drug designers are synthesizing single enantiomer products at the discovery stage itself to obtain 'cleaner drugs'. Since its introduction, organic chemists have taken advantage of the efficiency of DIP-Chloride in the syntheses of important pharmaceuticals.

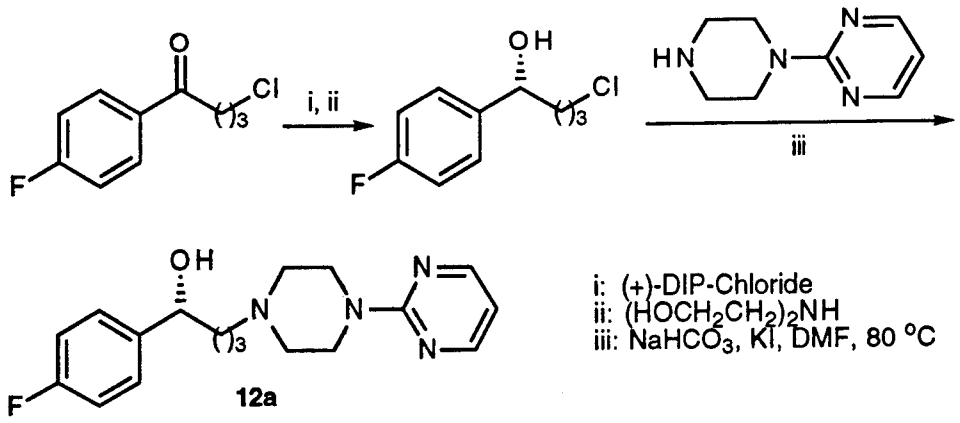
(a) Synthesis of an analog of a potential antipsychotic agent.

In the past, we have shown the utility of DIP-Chloride for the syntheses of opticlly pure enantiomers of Tomoxetine, Fluoxetine and Nisoxetine.[10] We have now synthesized an analog of a potential antipsychotic agent that is being clinically evaluated by Bristol-Myers-Squibb Co., α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol (BMS 181100, **12b**).[11]



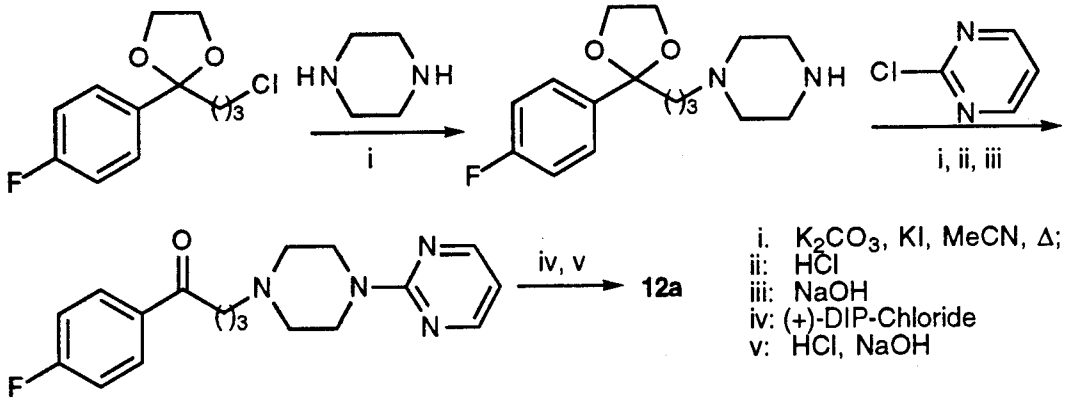
(*R*)-(+)-**12a**, X = H
(*R*)-(+)-**12b**, X = F (BMS 181100)

The published multistep synthesis of optically pure **12b** is very lengthy and cumbersome which involves a chiral resolution with α-methylbenzyl isocyanate providing a 7% overall yield, based on the ketone. Our efficient asymmetric synthesis of an analog of BMS 181100 *via* chiral reduction is shown in Scheme 3. Thus, asymmetric reduction of 4-chloro-4'-fluorobutyrophenone with (+)- or (–)-DIP-Chloride provides the corresponding (*R*)- or (*S*)-alcohol, respectively, in 90% isolated yield in 98% ee as determined by the analysis of its MTPA ester on a capillary column using a gas chromatograph. Coupling this with 2-(1-piperazinyl)pyrimidine prepared according to the literature procedure[12] yields 72% of **12a**.[13]



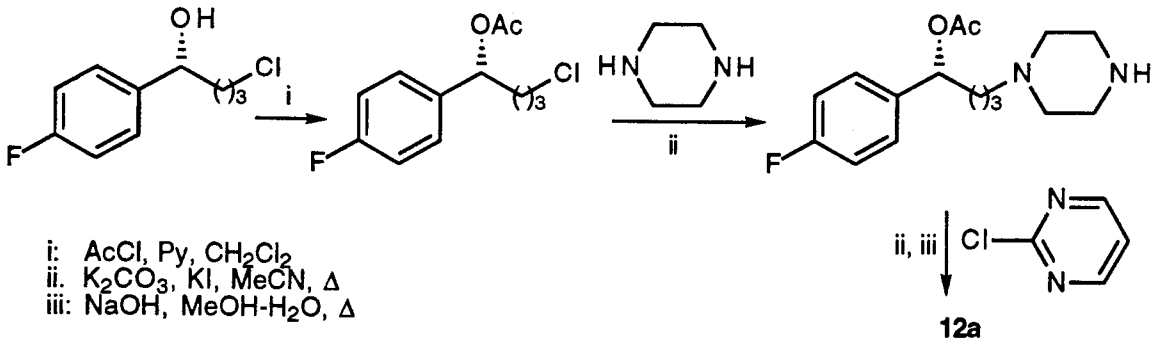
Scheme 3. Asymmetric synthesis of an analog of BMS 181100

Alternately, we synthesized **12a** *via* the reduction of the corresponding ketone. Due the coordination of the pyrimidinyl nitrogen with the boron of the reagent, we used three equiv of the reagent for the reduction. Yet, the reaction was very slow and the yields were poor.[14]



Scheme 4. Asymmetric aynthesis of an analog of BMS 181100 (method 2)

Since the above procedure is not appealing due to the need for excess reagent for the reduction as well as the poor yields and less than optimal ee of the product, we modified the step-wise coupling by employing R-α-(3-chloropropyl)-4-fluorobenzenemethylacetate to prepare **12a** in excellent yield (Scheme 5). Accordingly, the reaction of the chloroacetate with piperazine provided the piperazinyl acetate in 97% yield which was then coupled with 2-chloropyrimidine and deprotected to render **12a** in 77% overall yield and in ≥98% ee. The reaction of the unprotected alcohol contributes to the poor yield of the corresponding products in both coupling steps.

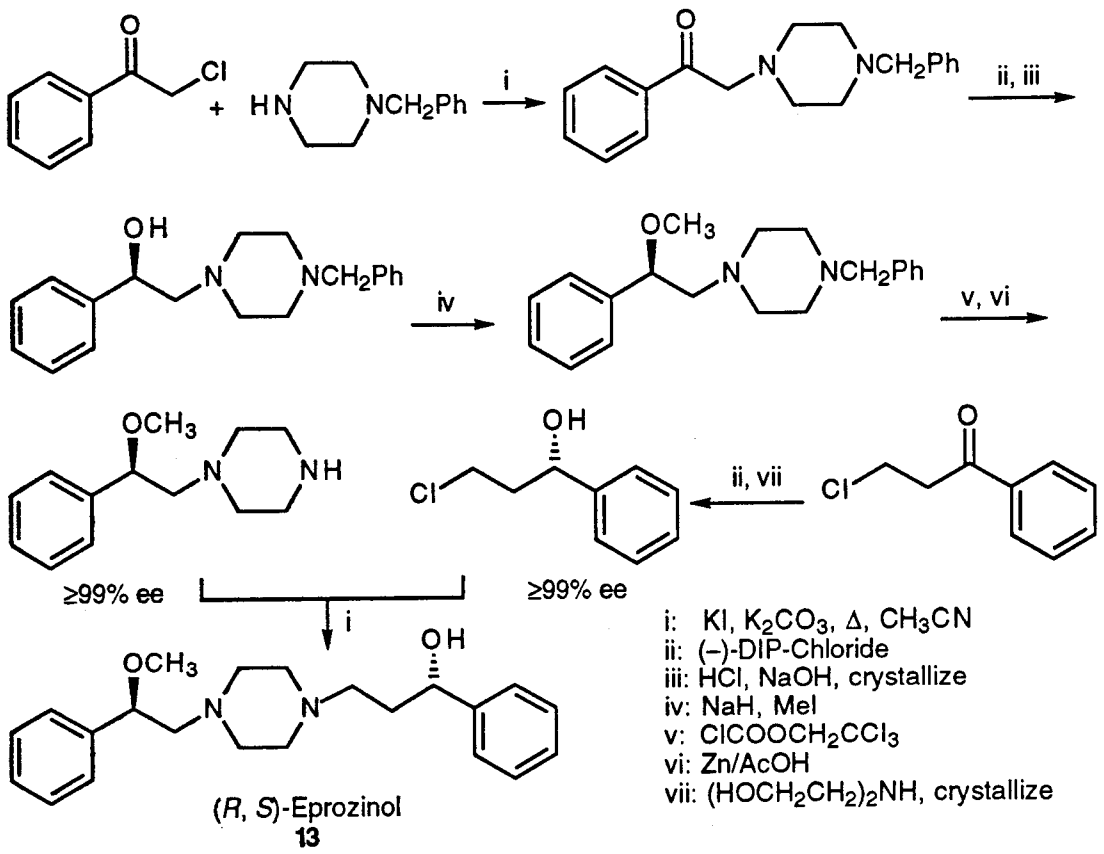


Scheme 5. Improved synthesis of (+)-(R)-α-(4-fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol

This procedure can be applied for the synthesis of either enantiomer of **12b**. Apart from increasing the yield, an added advantage of applying the latter method for the synthesis of **12b** will be that the difficult synthesis of 5-fluoro-2-(1-piperazinyl)pyrimidine can be avoided.

(b) Synthesis of Eprozinol

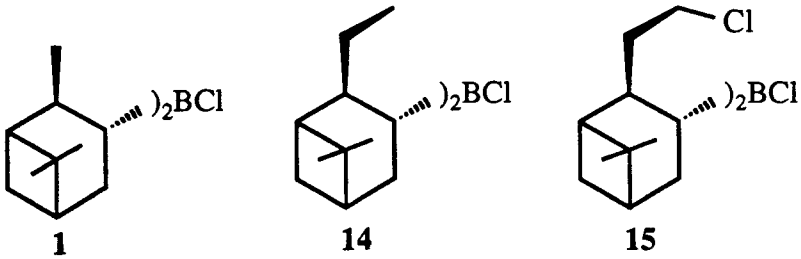
1-(2-Methoxy-2-phenethyl)-4-(3-hydroxy-3-phenylpropyl)piperazine (Eprozinol, **13**) has found use as a bronchodilator. As part of our program demonstrating the utility of DIP-Chloride for the synthesis of optically pure pharmaceuticals, we achieved the synthesis of this drug as outlined in the scheme below.[14] The asymmetric reductions of two aralkyl ketones provide the key chiral intermediates. Using this method all the four diastereomers can be prepared in pure form.



Scheme 6. Synthesis of enantiomerically pure Eprozinol via reduction with DIP-Chloride

3. Synthesis of a new efficient chiral reducing agent.

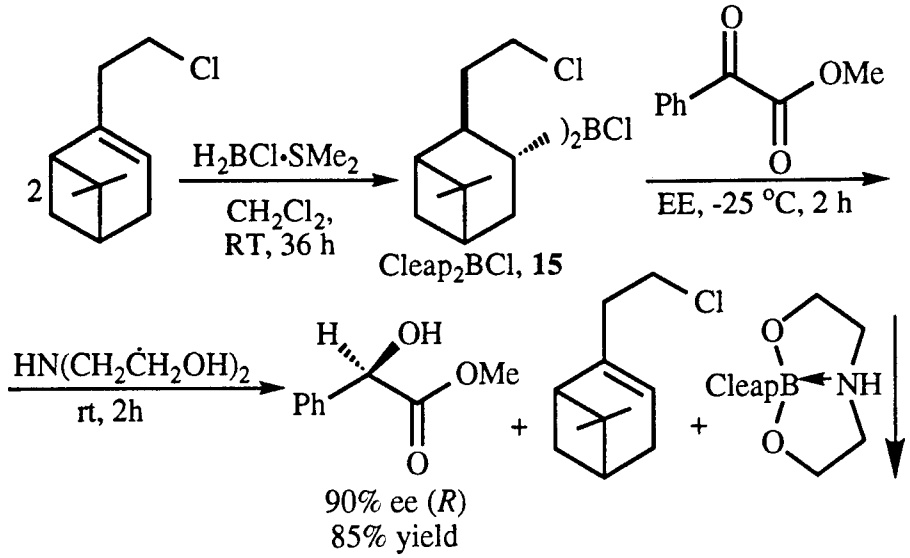
We continued our search for a chiral reducing agent that can reduce all classes of ketones.[15] Based on our hopothesis that the steric requirements of the alkyl group at the 2-position of apopinene controls the chiral induction, we synthesized diiso-2-β-chloroethylapopinocampheylborane (Cleap$_2$BCl, **15**) from nopyl chloride and chloroborane and tested it for the reduction of the standard ketones.



1 **14** **15**

A comparison of the reduction with **15** against DIP-Chloride and *B*-chlorodiiso-2-ethylapopinocampheylborane (Eap$_2$BCl, **14**)[16] is presented in Table 1. In addition to the asymmetric

reduction of the ketones that are successfully achieved with **1** and **14**, reagent **15** proved highly successful for the reduction of α-keto esters (Scheme 7).[17]



Scheme 7. Synthesis and reaction of $Cleap_2BCl$

Table 11. Asymmetric Reduction of Prochiral Ketones with R*$_2$BCl at –25 °C

class of ketone[15]	ketone	%ee		
		Ipc_2BCl	Eap_2BCl	$Cleap_2BCl$
1	acetylcyclohexane	26	97	≥99
2	2,2-dimethylcyclopentanone	98[a]	≥99[a]	≥99[a]
3	acetophenone	98	≥99	≥99
4	acetylpyridine	92	≥99	≥99[b]
5	2-chloroacetophenone	95	≥99	95[b]
6	methyl benzoylformate	50	70	90
7	ethyl benzoylacetate	no reduction		
8	*trans*-4-phenyl-3-butene-2-one	81	82	
9	2-cyclohexen-1-one	36	74	80[b]
10	4-phenyl-3-butyn-2-one	21	33	66

[a]For a reaction at rt. [b]For a reaction at 0–>10 °C.

$Cleap_2BCl$ proved to be exceptionally effective for the reduction of acetylcyclohexane (Class 1) and revealed a significant improvement of the earlier two reagents for the reduction of methyl benzoyl formate (Class 6), and 4-phenyl-3-butyn-2-one (Class 10). Consequently, we continue to

make excellent progress in our development of a general asymmetric reducing agent, capable of handling all 10 classes of ketones.

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III. List of Publications

This is a continuation of the list submitted with the last Final Report, Grant DAAG 29-88-K-0107, for the period 7/14/88 - 7/14/91. The required number of reprints of the publications 1-4 had been included in the semi-annual Reports. 15 copies of each of the publications 5-10 has been sent by separate post. Reprint of publication #11 is not yet available.

1. Asymmetric Reduction With Chiral Organoboranes Based on α-Pinene.
   Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.
2. Chiral Synthesis via Organoboranes. 34. Selective Reductions. 47. Asymmetric Reduction of Hindered α,β-Acetylenic Ketones With B-Chlorodiisopinocampheylborane to Propargylic Alcohols of Very High Enantiomeric Excess. Improved Workup Procedure for the Isolation of Product Alcohols.
   Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379.
3. Chiral Synthesis *via* Organoboranes. 38. Selective Reductions. 48. Asymmetric Reduction of Trifluoromethyl Ketones by *B*-Chlorodiisopinocampheylborane in High Enantiomeric Purity.
   Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725.
4. Asymmetric Synthesis of Both Enantiomers of α-(4-Fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol: Potential Antipsychotic Agents
   Ramachandran, P. V.; Gong, B.; and Brown, H. C. *Tetrahedron: Asym.* **1993**, *4*, 2399.
5. Recent Advances in the Boron Route to Asymmetric Synthesis.
   Brown, H. C.; Ramachandran, P. V. *Pure and Appl. Chem.* **1994**, *66*, 201.
6. A Remarkable Inversion in Configuration of the Product Alcohols from the Asymmetric Reduction of *ortho*-Hydroxyacetophenones with *B*-Chlorodiisopinocampheylborane·
   Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141.
7. Selective Reductions. 52. Efficient Asymmetric Reduction of α-Acetylenic α'-Fluoroalkyl Ketones with Either Diisopinocampheylchloroborane or *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane. The Influence of Electronic Factors in Reduction.
   Ramachandran, P. V.; Gong, B.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron: Asym.* **1994**, *5*, 1061.
8. Selective Reductions. 53. Asymmetric Reduction of α-Fluoromethyl Ketones with Diisopinocampheylchloroborane and *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane. Combined Electronic and Steric Contributions to the Enantiocontrol Process.
   Ramachandran, P. V.; Teodorovic, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asym.* **1994**, *5*, 1075.
9. An Approach to a General Reagent For Asymmetric Reduction.

Ramachandran, P. V.; Brown, H. C. in *Current Topics in the Chemistry of Boron*, Kabalka, G. Ed. The Royal Society of Chemistry Special Publication No. 143, Cambridge, U. K., **1994**, pp 101-112.

10. Recent Advances in the Boron Route to Asymmetric Synthesis.
Brown, H. C.; Ramachandran, P. V. in *Current Topics in the Chemistry of Boron*, Kabalka, G. Ed. The Royal Society of Chemistry Special Publication No. 143, Cambridge, U. K., **1994**, pp 125-128.

11. Asymmetric Synthesis *via* Chiral Organoboranes Based on α-Pinene.
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